CRITICAL CARE

COMMENTARY

Hypertonic saline, not mannitol, should be considered gold-standard medical therapy for intracranial hypertension

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Abstract

Hyperosmolar therapy is the principal medical management strategy for elevated intracranial pressure. Mannitol has been the primary hyperosmolar agent for nearly a century and remains the *de facto* gold standard for medical management of intracranial hypertension. Over the past 25 years, however, hypertonic saline (HTS) has become a progressively more common alternative to mannitol, and several recent studies have suggested its relative superiority. These findings have prompted calls for large-scale comparator trials of mannitol and HTS, but such trials would only be necessary if the designation of mannitol as the gold standard is appropriate and if current evidence suggests its therapeutic equipoise with HTS. Mounting evidence supporting HTS suggests that neither of these conditions is necessarily true and, instead, mandates reassessment of the actual gold-standard agent for hyperosmolar therapy. In the present article I make the case that current evidence supports HTS, not mannitol, as the better choice for gold-standard therapy for medical management of intracranial hypertension. This is accomplished first by examining the evidence on which the apparent designation of mannitol as the presumed gold-standard is based, then by reviewing the recent comparative efficacy data for HTS versus mannitol, and finally by discussing additional clinical considerations for appropriate designation of a gold-standard agent for hyperosmolar therapy. This assessment has important implications both for patient care and for clinical trial design.

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Introduction

Hyperosmolar therapy with mannitol or hypertonic saline (HTS) is the primary medical management strategy for elevated intracranial pressure (ICP) [1]. Although both agents have been used for nearly a century [1-3], mannitol predominated through the 1980s [2,3] and remains the *de facto* gold standard for medical management of intracranial hypertension (IH) [4,5].

Several recent studies suggest the relative superiority of HTS to mannitol [3,6,7], prompting calls for large-scale comparator trials. Such trials are only necessary if the designation of mannitol as the gold standard is appropriate and if current evidence suggests its therapeutic equipoise with HTS. Mounting evidence supporting HTS suggests that neither of these conditions is necessarily true and, instead, mandates reassessment of the gold-standard agent for hyperosmolar therapy.

In the present commentary I argue that current evidence supports HTS, not mannitol, as the better choice for gold-standard therapy for medical management of IH. I make this argument first by examining the evidence on which the apparent designation of mannitol as the current gold standard is based. Next, I review recent comparative efficacy data for HTS versus mannitol. Finally, I discuss additional clinical considerations for appropriate designation of a gold standard. This assessment has important implications both for patient care and for clinical trial design.

Evidence supporting mannitol

Much of the literature regarding mannitol is reported from the trauma population and is subsequently generalized to other cohorts. Two comprehensive reviews have summarized this evidence. The first, a Cochrane review [8], identifies four studies supporting the efficacy of mannitol in treating IH. Two of these four studies directly compare outcomes in patients receiving mannitol with those of control patients (treated with phenobarbital or placebo). One of these studies represents class I evidence (n = 20) and the other is a class III investigation (n = 31).

The second comprehensive analysis is a review by the Neurotrauma Society in its brain injury guidelines [4]. This review identifies seven additional studies supporting the efficacy of mannitol, of which one study is class II and the remainder are class III.

Together, these two reviews identify a total of nine clinical studies of appropriate quality supporting the use of mannitol for treatment of IH. The class I evidence supporting mannitol is limited to one study of 20 patients, with additional validation provided by class II and class III investigations. While other preclinical and clinical studies report the use of mannitol, these nine studies represent the highest-quality clinical evidence on which the designation of mannitol as the gold-standard treatment for IH is based.

Evidence supporting hypertonic saline

Evidence for the independent efficacy of HTS therapy for IH has recently been reviewed [6]. A total of 36 studies describe HTS treatment of IH in adults and children from etiologies including trauma, stroke, tumor, infection, and intracranial and subarachnoid hemorrhage. These comprise 10 class I studies, 16 class II studies, and 10 class III studies. Subset analysis demonstrates successful ICP reduction in 15 of 16 studies involving traumatic brain injury (n = 349), in 10 of 11 studies involving nontraumatic injury (n = 266), in eight of nine studies involving mixed injuries (n = 208), and in five of five studies involving pediatric patients (n = 195). Although treatment protocols for administering HTS vary, the authors report that ICP reductions are independent of the dosage or the administration strategy [6].

The present review also examines a subset of 12 studies (n = 296) directly comparing HTS with mannitol therapy [6]. This subset includes seven class I studies, one class II study, and four class III studies. Although varying in methodology, nine of the 12 studies (including five class I studies) demonstrate that HTS provides 'superior control of ICP over mannitol' [6]. Additionally, data from 230 treatment failures demonstrate a lower failure rate in patients treated with HTS versus those managed with mannitol (16% vs. 35%, odds ratio = 0.36, P = 0.002). Finally, separate data demonstrate that HTS is successful in controlling ICP when mannitol fails [1].

A recent meta-analysis quantifies the comparative efficacy of the two agents [7]. This study aggregates data from randomized clinical trials (all class I) directly comparing mannitol and HTS in adults with IH from various etiologies (as above). The authors identify five trials comprising 112 patients with 184 episodes of elevated ICP and report an ICP control rate of 93% for patients managed with HTS versus 78% for patients treated with mannitol. The pooled relative risk of ICP control with HTS relative to mannitol was 1.16 to 1.20 (P = 0.07 to 0.046, specific values are model dependent), and the weighted mean difference in ICP reduction between the two agents was 2.0 mmHg (P = 0.036).

Together, these two studies [6,7] compile the results of 37 primary investigations, of which 11 represent class I evidence. The independent efficacy of HTS is summarized by Mortazavi and colleagues, who report successful ICP reduction in the vast majority of investigations and clinical scenarios [6]. The two studies also report a total of 13 direct comparisons between HTS and mannitol, of which eight are class I. Both studies demonstrate the comparative superiority of HTS [6,7], and the meta-analysis quantifies this effect and verifies its statistical significance [7].

Defining a gold standard

Superior efficacy is a necessary but not sufficient criterion for defining a gold-standard therapy, and at least two additional factors must be considered. First, barring prohibitive logistical or cost considerations (which do not apply here), gold-standard therapies tend to be the most commonly used treatments for a particular condition. With regard to IH, a recent study demonstrates that the majority of experts in neurocritical care now prefer HTS to mannitol (55% vs. 45%) [9]. Second, a gold-standard therapy should ideally have a more favorable side-effect profile than its alternatives. The most common side effects of mannitol – osmotic diuresis and acute kidney injury [1,10] – are much less common among patients treated with HTS [1]. Unlike mannitol [1], the overall rate of serious adverse events associated with HTS is exceedingly low [1,6]. These observations, along with the demonstrable independent efficacy of HTS and its superior comparative efficacy versus mannitol, argue in favor of HTS as the gold-standard medical therapy for elevated ICP.

Conclusions

Mannitol is often considered the gold-standard therapy for medical management of IH, primarily because of its long history. The data presented in this commentary suggest that history may be the only factor favoring such a designation. While the efficacy of both agents for ICP reduction has been demonstrated [1], the relatively small amount of actual class I evidence supporting mannitol pales in comparison with that of HTS. Additionally, numerous class I comparisons and a recent meta-analysis thereof have demonstrated the superior comparative efficacy of HTS over mannitol. Moreover, this discussion illustrates that small sample size and variable administration strategies – the common criticisms of HTS studies [3] – are not compelling. With regard to sample size, the number of patients reported in high-quality trials of HTS actually exceeds the comparable number

supporting mannitol. With regard to variability of dosage and administration strategies, Mortazavi and colleagues suggest they are clinically irrelevant [6]. Finally, HTS is currently the preferred agent of a majority of neurointensivists, and it is associated with a more favorable side-effect profile than mannitol.

This discussion is not intended to dispute the efficacy or the therapeutic value of mannitol. Notwithstanding, if either of these two agents is to be considered the gold-standard medical therapy for IH, the preponderance of current evidence suggests that it be HTS, not mannitol. This, in turn, will allow the considerable cost and effort of large-scale clinical trials to be directed towards questions to which the answers are not already evident.

Abbreviations

HTS, hypertonic saline; ICP, intracranial pressure; IH, intracranial hypertension.

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Conflicts of interest

The author declares that he has no competing interests.

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References

1. Torre-Healy A, Marko NF, Weil RJ: **Hyperosmolar therapy for intracranial hypertension.** *Neurocrit Care* 2011 Nov 17. [Epub ahead of print]
2. Strandvik GF: **Hypertonic saline in critical care: a review of the literature and guidelines for use in hypotensive states and raised intracranial pressure.** *Anaesthesia* 2009, **64:**990-1003.
3. Kerwin AJ, Schinco MA, Tepas JJ, 3rd, Renfro WH, Vitarbo EA, Muehlberger M: **The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study.** *J Trauma* 2009, **67:**277-282.
4. **Guidelines for the management of severe traumatic brain injury.** *J Neurotrauma* 2007, **24(Suppl 1):**S1-S106.
5. Stubbe HD: **Salt or sugar on the brain: does it matter except for taste?** *Crit Care Med* 2011, **39:**601-602.
6. Mortazavi MM, Romeo AK, Deep A, Griessenauer CJ, Shoja MM, Tubbs RS, Fisher W: **Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis.** *J Neurosurg* 2012, **116:**210-221.
7. Kamel H, Navi BB, Nakagawa K, Hemphill JC, 3rd, Ko NU: **Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials.** *Crit Care Med* 2011, **39:**554-559.
8. Wakai A, Roberts Ian G, Schierhout G: **Mannitol for acute traumatic brain injury.** *Cochrane Database of Systematic Reviews* 2007, **1:**CD001049.
9. Hays AN, Lazaridis C, Neyens R, Nicholas J, Gay S, Chalela JA: **Osmotherapy: use among neurointensivists.** *Neurocrit Care* 2011, **14:**222-228.
10. Hinson HE, Stein D, Sheth KN: **Hypertonic saline and mannitol therapy in critical care neurology.** *J Intensive Care Med* 2011 Mar 24. [Epub ahead of print]

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